VISUS Therapeutics
Protocol #: VT-002

A 3-Arm, Multicenter, Randomized, Double-Masked, Crossover Safety and Efficacy Study of BRIMOCHOL™ PF (Carbachol/Brimonidine Tartrate Fixed-Dose Combination) Topical Ophthalmic Solution vs. Carbachol PF Monotherapy Topical Ophthalmic Solution vs. Brimonidine Tartrate Monotherapy Topical Ophthalmic Solution in Subjects with Emmetropic Phakic or Pseudophakic Presbyopia

Statistical Analysis Plan

Version 2
04Apr2023

[redacted]

[redacted]

Visus Therapeutics, Inc.

[redacted]

Visus Therapeutics, Inc.

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I. Introduction

A. Background

Presbyopia is an inevitable, age-related, gradual loss in the ability to focus at intermediate and near targets without spectacle or surgical correction due to a progressive loss of elasticity in the crystalline lens. Pharmacologic miosis with cholinergic agents such as pilocarpine has been well-established to improve near visual acuity and depth of focus in presbyopic individuals, but the duration of action has been limited.

Visus Therapeutics, Inc. (Visus) is developing BRIMOCHOL™ PF (Preservative Free) (carbachol 2.75% / brimonidine tartrate 0.1% fixed-dose combination) Topical Ophthalmic Solution (hereafter BRIMOCHOL PF) and Carbachol PF 2.75% Monotherapy Topical Ophthalmic Solution (hereafter Carbachol PF) eye drops for improvement in near visual acuity in emmetropic phakic and pseudophakic presbyopia.

The present study has been designed as a crossover study to compare the safety and efficacy of the

The protocol describes the general approach to analysis of data from the study. This analysis plan describes additional detail needed to complete such an analysis.

B. Version History

The table below identifies all sign-off SAP versions and the corresponding protocol version that is supported by each SAP version. In addition, if any analytical method in the SAP deviates from the protocol, the changes will be captured.

SAP Version	Protocol Version (Date)	Changes from Protocol*
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted].

This SAP will govern the analysis of data from this study. The plan may be modified until the time of treatment unblinding. Any deviations from the analysis plan, including any after the time of treatment unblinding, will be documented as such in the study report.

II. Protocol Objectives

The main objectives of this study are:

- To demonstrate the efficacy, safety, tolerability, [redacted] of the fixed-dose combination BRIMOCHOL PF (Carbachol PF 2.75%/brimonidine tartrate 0.1% fixed-dose combination) compared with its individual components: Carbachol PF 2.75% monotherapy and brimonidine tartrate 0.1% monotherapy (also PF) topical ophthalmic solutions in subjects with emmetropic phakic or pseudophakic presbyopia

- To evaluate the pharmacodynamic effect on pupil size of the fixed-dose combination BRIMOCHOL PF compared with the individual components Carbachol PF 2.75% monotherapy and brimonidine tartrate 0.1% monotherapy topical ophthalmic solutions in subjects with emmetropic phakic or pseudophakic presbyopia

III. Study Endpoints

A. Efficacy Endpoints

Primary Efficacy Endpoints for the US FDA

A treatment responder is defined as a subject who has a ≥15 Early Treatment of Diabetic Retinopathy Study (ETDRS) letter gain from Baseline in Binocular Uncorrected Near Visual Acuity (BUCNVA) without a ≥5 ETDRS letter loss in Binocular Uncorrected Distance Visual Acuity (BUCDVA) using both eyes under mesopic conditions. Baseline at each dosing visit will be the pre-dose assessment at Hour 0 of the visit. [redacted]

1) The efficacy superiority of BRIMOCHOL PF over the monotherapies will be demonstrated if BRIMOCHOL PF has a statistically significantly greater responder rate than Brimonidine Tartrate and Carbachol PF at Hour 1.

2) Assuming that the efficacy superiority of BRIMOCHOL PF over both monotherapies is established at Hour 1, [redacted]

Primary Efficacy Endpoint for Rest of the World (ROW)

For each subject, an area under the curve ($AUC_{0\text{-}8h}$) at a visit is defined as a weighted average of changes from Baseline in ETDRS letters of BUCNVA using [redacted] The specific calculation algorithm of the AUC based on the trapezoidal rule is provided in Appendix B.

- The efficacy superiority of BRIMOCHOL PF over both monotherapies will be established if BRIMOCHOL PF has a statistically significantly greater mean AUC than both monotherapies.

[redacted]

[redacted]

B. Pharmacodynamic Endpoints

- Change from Baseline in pupil size in each eye, the average, the minimum, and the maximum of the two eyes at all timepoints for mesopic measurements

[redacted]

C. Safety Endpoints

- Ocular and non-ocular Adverse Events (AEs), Slit-Lamp Biomicroscopy, Intraocular Pressure (IOP), Dilated Ophthalmoscopy

- Proportion of subjects with a $\geqslant$15 letters loss in mesopic MUCNVA at 40 cm in either eye

- Proportion of subjects with a $\geqslant$15 letters loss in mesopic BUCDVA at 4 M using both eyes

[redacted]

IV. Study Design

A. Design Overview

This is a 3-treatment, multicenter, randomized, crossover, Phase 3 safety and efficacy study [redacted] with visually significant emmetropic phakic or pseudophakic presbyopia, and until approximately 152 subjects complete the study at study sites in the United States.

After signing the Informed Consent Form (ICF) and meeting all eligibility criteria at the Screening Visit [redacted] subjects will be randomly assigned to one of the treatment sequences that include each of the three study treatments. Subjects will receive each study treatment once in order [redacted]

The study visits are:

- Visit 1 (-14 to -1 days): [redacted]
- Visit 2: [redacted]
- Visit 3: [redacted]
- Visit 4/Exit: [redacted]

B. Study Population

[redacted] with visually significant emmetropic phakic or pseudophakic presbyopia and until approximately 152 subjects complete the study.

C. Sample Size Consideration

Sample size and power consideration is based on the procedure given by Connor (1987). The response rates of a paired population are denoted in the table below:

	Test Group		Total
	[redacted]	[redacted]	

[redacted]

D. Treatment Randomization

Subjects will be randomly allocated to 1 of the following crossover treatment sequences:

[redacted]

E. Assessment Schedule

After the screening visit (Visit 1), the study period will include 3 treatment visits (Visit 2, 3, 4). Subjects will be required to attend all scheduled visits.

At each treatment visit, study drug will be instilled [redacted] Allowable post-dose assessments will be conducted

as follows: Hour 0.5 [redacted], Hour 1 [redacted], [redacted]. Pupillometry [redacted]. Slit-lamp biomicroscopy with corneal staining will be performed after all visual functional assessments are performed. Intraocular pressure (IOP) will be performed after the slit-lamp biomicroscopy. [redacted]

F. Interventions and Study Procedures

The study procedures for the key study outcomes are as follows:

1. ***Visual Function Assessments***: Visual acuity (VA) tests will be performed using the early treatment diabetic retinopathy study (ETDRS) charts, [redacted] The table below shows the characteristics of each visual function assessment performed

Table 1: Summary of Visual Function Assessments

[redacted]

[redacted]

2. ***Pupillometry***: An objective pupillometer will be used to measure the diameter of the pupil [redacted] The following results will be reported for each eye at each timepoint:

   - Mean diameter (mm) of the pupil [redacted]
   - Standard deviation (mm) of the pupil [redacted]

3. [redacted]

4. ***Ocular Health Assessments***: Ocular Health will be assessed with slit-lamp biomicroscopy, intraocular pressure (IOP (mm Hg)), and dilated ophthalmoscopy

   - Slit-lamp Biomicroscopy: Assessments with corneal staining will be performed at the screening visit and visit 2, 3, 4 [redacted] Slit-lamp biomicroscopy findings of the Conjunctiva, Cornea, Iris/Pupil, Lens are categorized as: 1) Normal, 2) Abnormal, Not Clinically Significant and 3) Abnormal, Clinically Significant. Cell grade/Anterior chamber findings are categorized as 0, 0.5: 1-5,1: 6-15, 2: 16-25, 3: 26-50, and 4: > 50. [redacted]

[redacted]

- IOP (OD/OS): Assessments will be performed at the screening visit and visit 2, 3, 4 after the slit-lamp biomicroscopy assessments are performed.

- Dilated Ophthalmoscopy (OD/OS): Assessments will be performed at the screening visit and at visit 4 after the final visual functional evaluation. Ophthalmoscopy findings of the Macula, Retina/Choroid, Vitreous, Lens and Optic nerve are categorized as: 1) Normal, 2) Abnormal, Not Clinically Significant and 3) Abnormal, Clinically Significant.

V. General Analytical Considerations

A. Data Sources

Data are recorded on electronic case report form (eCRF) for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to the Sponsor and regulatory authorities, as applicable. Kit assignment and randomization are conducted by [redacted] (IRT). Pupillometry data and visual function data are collected [redacted]

All statistical analysis will be performed using SAS Version 9.4 or higher with program code prepared specifically for the project by qualified statisticians and SAS programmers.

All observed and derived variables that are analyzed or summarized will be listed by subject. Descriptive statistics will provide an overview of the efficacy and safety results. For categorical parameters, the number and percentage of subjects in each category will be presented. For continuous parameters, descriptive statistics will include number of subjects, mean, SD, median, minimum, and maximum.

B. Definition of Baseline

Date of Visit 2 is defined as Day 1, which is the date of first study drug administration at the randomization visit. Study day will be calculated relative to the date of Day 1.

[redacted]

[redacted]

The screening visit baseline will be applied for vital signs, IOP, biomicroscopy and ophthalmoscopy assessments. Change from baseline at each visit will be calculated as the value at the visit minus the value at the screening visit.

C. Multiple Records at a Timepoint

Visual acuity and pupillometry are assessed at multiple timepoints [redacted] at each visit. Sometimes these measurements are taken multiple times at a timepoint. For analysis purposes, the convention is to use the last recorded values to represent each timepoint.

[redacted]

D. Analysis Visit Window

All efficacy and safety endpoints will be summarized and analyzed according to their nominal visit. Unless otherwise specified, data of unscheduled visits will not be considered for the by-visit summary statistics but will be included in the by-subject listings.

E. [redacted]

[redacted]

[redacted]

[redacted]

F. Multiple Comparisons

For the US FDA

[redacted]

For the ROW

[redacted]

G. Analysis Populations

Several analysis populations are defined for use with various analyses.

- **Safety Population (SAF)**

  All enrolled subjects who received at least 1 dose of study drug will be included in the Safety population. Subjects will be analyzed as treated.

- **Modified Intent-to-treat (mITT) Population**

  The mITT population will include all randomized subjects who received at least 1 dose of study drug at Visits 2, 3, or 4. Subjects will be analyzed as randomized.

- **Per-Protocol (PP) Population**

  The per-protocol population is the subset of mITT population for whom no major protocol deviation that may affect the primary efficacy endpoint is documented. [redacted]

H. Data Display Characteristics

Data displays produced for this study will include three types - summary tables, data listings, and figures. Unless stated otherwise, data listings will be produced for all recorded data. Summary tables will be produced as specified in following sections. Additional data listings will be produced for outcome measures that involve extensive procedures to derive the analyzed outcomes. Figures will be produced when specified in sections to follow.

Data listings will simply list the data collected in the database or derived for each subject. In general, they will be ordered by treatment (if applicable) subject number, visit and time of assessment. When expedient, additional levels of ordering hierarchy may reflect subsets of assessments within subject. The treatment associated with each visit will be included in all listings. For listings with monocular assessments, results of the right eye will be presented first.

Summary tables will display summary statistics calculated for each of the treatments and by timepoint, unless described otherwise in following sections.

[redacted]

[redacted]

VI. Subject Accountability and Characteristics

A. Baseline Characteristics

Baseline characteristics will be summarized in one group of all subjects without treatment groupings.

Subject Characteristics: The following subject characteristics at the screening visit will be summarized in each analysis population [redacted]:

- Age (years)
- Age group (≤ 53 vs. > 53 years)
- Sex
- Race
- Ethnicity

Ocular Characteristics: Data will be summarized for all subjects in each analysis population [redacted]

[redacted]

Medical/Ocular History: Medical/Ocular history will be summarized for all subjects in the mITT population. Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA Version 24) and summarized by system organ class (SOC) and preferred term (PT). Ocular history will be summarized for each eye. Ocular history involving both eyes will be counted for each eye separately.

B. Disposition and Subject Accountability

Subject disposition will be summarized as one group for all screened subjects, the numbers of subjects who were screened, randomized, and either completed the

study or prematurely withdrew from study participation. Study completion will be indicated by the response "Yes" on the study completion status form. Any other response on this form will be counted as a premature withdrawal.

Premature withdrawals will be further characterized as the number of subjects who withdrew prematurely for each of the following reasons listed on the study completion status form:

- Adverse Event
- Death
- Lack of Efficacy
- Lost to follow-up
- Non-compliance with study drug
- Physician Decision
- Pregnancy
- Protocol Deviation
- Study terminated by sponsor
- Withdrawal by Subject
- Other

Percentages of subjects who withdrew for each of these reasons will be calculated using all members of the relevant population for the denominator. Subjects in each analysis population will be summarized.

[redacted]

[redacted]

C. Protocol Deviations

The sponsor will review and determine major protocol deviations prior to database lock. A summary table will be used to report the number and percentage of subjects with major protocol deviations. All reported protocol deviations will be listed.

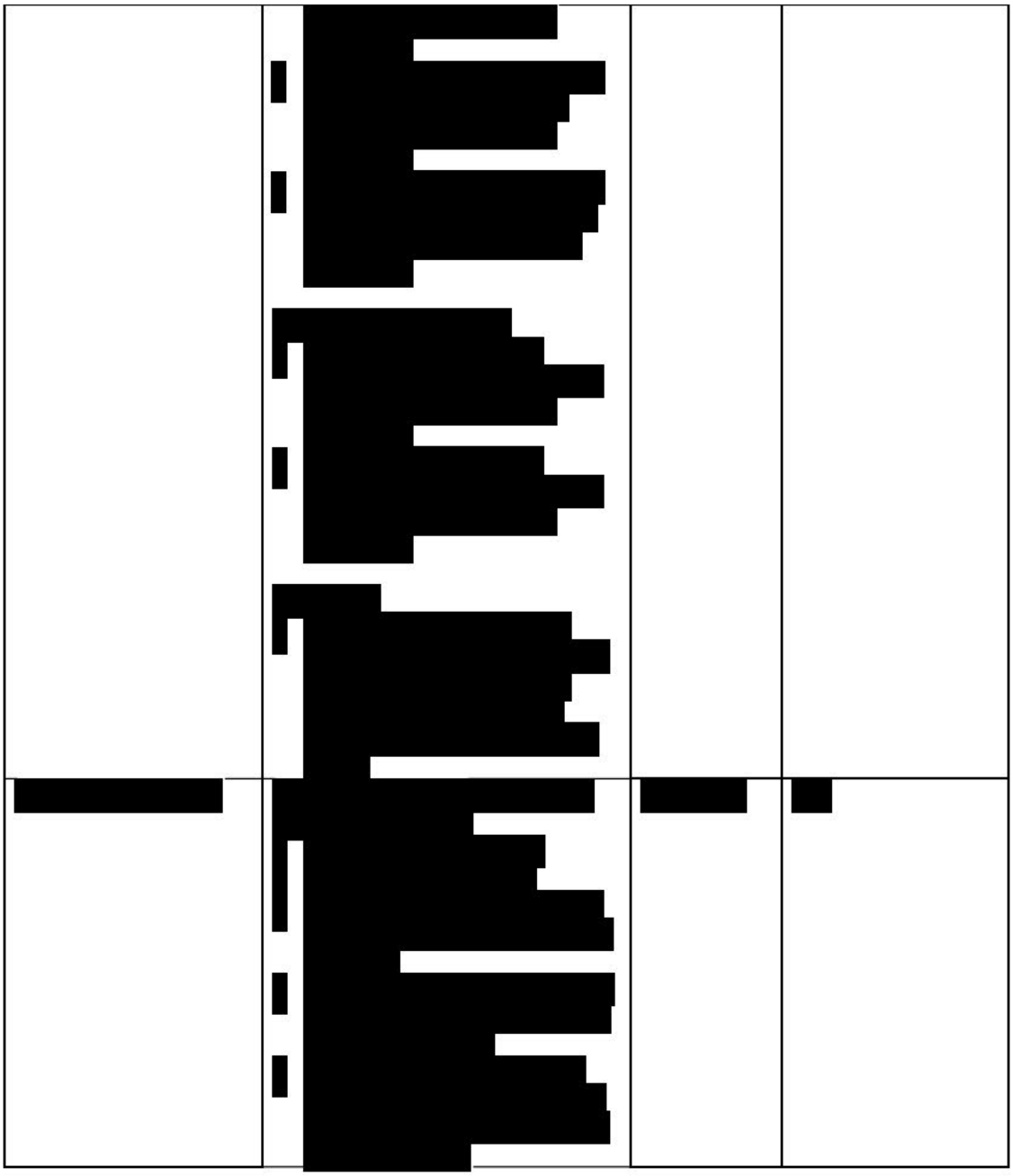
VII. Efficacy Analyses

[redacted]

A. Summary of Efficacy Analyses

All planned efficacy analyses are outlined in the table below, followed by detailed explanations in Sections VII.B through VII.F.

Table 2: Summary of Efficacy Analyses



B. Primary Efficacy Outcome Analysis

B.1 For the US FDA

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

B.2 For the ROW

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

VIII. Pharmacodynamic Analyses

[redacted]

[redacted]

IX. Safety Analyses

Safety analyses will be performed based on the Safety population.

A. Adverse Events

Adverse events will be coded using the MedDRA dictionary version 24.
AE summaries will include treatment-emergent AEs (TEAEs), that is, AEs with an onset date or worsening in severity on or after the date of any study treatment administration, but prior to the administration of the subsequent study treatment if

applicable.

Missing AE start date will be imputed using the following algorithm:

- If completely blank, assume January 01 and year of the stop date (if available) or the year of screening visit date (otherwise).
- If only year is recorded, assume January 01 for the missing month and day.
- If only month and year are recorded, assume 01 for the missing day.

Missing AE stop date will be imputed using the following approach:

- If completely blank, assume the day of the last study visit.
- When only year is recorded, assume the 31st December for the missing date or the date of the last study visit (whichever is earlier).
- If only month and year are recorded, assume the last day of the month or the date of the last study visit (whichever is earlier).

The relationship and the severity of adverse event will be determined by the investigator. Adverse events are classified as related to the study drug if they are "possible related", "probable related" and "definite related" collected in CRF. The detailed classification of the relationship and severity of adverse event is in Protocol Section 9.2.3 and 9.2.4.

If the relationship to study drug is missing, the event will be conservatively summarized as being related to the study drug. If severity is missing, a separate category of missing severity will be included in the summary table, and no imputation of severity will be performed. Through the data cleaning process, all attempts will be made to avoid missing values for relationship and severity.

AEs will be summarized by treatment and overall, as incidence rates of:

- All AEs
- All SAEs
- All TEAEs
- All Ocular TEAEs
- All Non-ocular TEAEs
- All Serious TEAEs
- Deaths

- Ocular Events of Special Interest
  - Per protocol, ocular events of special interest are defined as events with (1) Acute angle glaucoma or moderate to severe increase in IOP of >25 mm Hg or (2) Retinal tear or detachment.
  - The adverse event of special interest flag collected in CRF will be used to select the ocular events of special interest.

- Treatment-related TEAEs
  - This table will include TEAEs with a drug relationship of “Possible,” “Probable,” and “Definite”.

- TEAEs leading to study withdrawal
  - This subset includes TEAEs with an Action Taken of “Permanent Discontinuation”.

- TEAEs by maximum severity
  - On this table, treatment groups will be subdivided into four potential grades of AE severity— Mild, Moderate, Severe, Potentially Life threatening. Subjects reporting multiple AEs with different severities will be summarized once in the most severe category.

In addition, the following AE summaries will be produced:

- All ocular TEAEs by preferred term (PT) in descending order of overall frequency
- All non-ocular TEAEs by system organ class (SOC) in alphabetical order and preferred term (PT) in descending order of overall frequency
- Serious TEAEs by SOC and PT
- Ocular events of special interest by PT
- TEAEs leading to study withdrawal by SOC and PT
- Treatment-related TEAEs by SOC and PT
- TEAEs by SOC, PT and maximum severity

At each level of summarization by SOC and PT, a subject with multiple events will be counted only once. No hypothesis test will accompany these AE summary tables.

All AEs will be listed by subject, detailing the verbatim term given by the investigator, PT, SOC, onset date, end date, severity, relationship to study drug, outcome, action taken, seriousness and criteria for seriousness, ocular event of special interest (Y/N), whether an AE is considered as a TEAE (Y/N), and if so, which study treatment is the TEAE attributed to.

B. Ocular Health Assessments

Visual acuity Assessments: Descriptive statistics will be used to summarize observed values and change from pre-dose baseline values in mesopic MUCNVA in each eye at all timepoints. [redacted]

Slit-lamp Biomicroscopy (OD/OS)*:* Assessments with corneal staining are performed after all visual function assessments at all visits. The findings of Conjunctiva, Cornea, Iris/Pupil, Lens, and Cell grades/Anterior chamber are collected at Visits 1, 2, 3, and 4. Findings of the Conjunctiva, Cornea, Iris/Pupil, and Lens are categorized as: 1) Normal, 2) Abnormal, Not Clinically Significant and 3) Abnormal, Clinically Significant. Cell grade/Anterior chamber findings are categorized as 0, 0.5: 1-5,1: 6-15, 2: 16-25, 3: 26-50, and 4: > 50. Shaffer grades are categorized as Grade 0: 0º, Grade 1: 10º, Grade 2: 20º, Grade 3: 20º-35º, Grade 4: 35º-40º. Changes from baseline (Visit 1) will be summarized using shift tables for each post-baseline visit. Corneal Staining grades of each of 5 corneal regions are assessed on the National Eye Institute (NEI) corneal grading scale (0-3). The total grade and change from baseline (Visit 1) will be summarized for each post-baseline visit. [redacted]

Ophthalmoscopy Assessments (OD/OS): Macula, Retina/Choroid, Vitreous, Lens and Optic nerve are assessed at Visit 1 and Visit 4 after the visual functional evaluation. Macula, Retina/Choroid, Vitreous, Lens and Optic nerve are categorized as: 1) Normal, 2) Abnormal, Not Clinically Significant and 3) Abnormal, Clinically Significant. Changes from baseline (Visit 1) at Visit 4 will be summarized by eye using shift tables.

Intraocular Pressure (IOP) (OD/OS): IOP (mm Hg) is assessed at Visits 1, 2, 3, and 4 after the slit-lamp biomicroscopy assessments are performed. Descriptive statistics will be used to summarize observed continuous values and changes from baseline (Visit 1) value in IOP by eye and by visit.

Manifest Refraction: Spherical Refractive Error (diopter, range +5.0 to –5.0), Cylindrical Refractive Error (diopter, range +5.0 to –5.0), Astigmatism Axis (degree, range 0 -180), and Spherical Equivalent (diopter, +7.5 to -7.5) which is equal to Spherical Reflective Error + half of Cylindrical Reflective Error) are collected during the screening. Data will be summarized by eye.

All ocular assessments in this section will be listed by subject.

C. Vital Signs

Vital signs measurements including temperature (ºC), respiratory rate (breaths/min), pulse rate (bpm), systolic blood pressure (mm Hg), and diastolic blood pressure (mm

Hg), at each scheduled visit and changes from the Screening visit will be summarized by treatment. All vital signs measurements will be listed by subject.

D. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug Version 01 September 2020 (Global, B3 format)

Missing medications start date will be imputed using the following approach:

- If completely blank, assume 01Janyyyy, where yyyy is the year of the Stop date (if available) or the year of Screening visit date (otherwise).
- If only year is recorded, assume 01Jan for the missing month and day.
- If only month and year are recorded, assume 01 for the missing day.

Missing medications stop date will be imputed using the following approach:

- If completely blank, assume the day of the last study visit.
- When only year is recorded, assume the 31Dec for the missing date or the date of the last study visit (whichever is earlier).
- If only month and year are recorded, assume the last day of the month or the date of the last study visit (whichever is earlier).

Prior medication: Any medication with a start date prior to the first dose of study drug is classified as a prior medication.

Concomitant medication: Any medication is classified as a concomitant medication if the start date is on or after the first dose of study drug or any prior medication (whose start date is before the first dose of study drug) which is ongoing after the first dose of study drug and then has an increase in either the dosage or the frequency. Thus, a prior medication ongoing after the first dose of study drug is NOT classified as a concomitant medication if it does not increase either the dosage or the frequency during the study.

Concomitant medications will be further attributed to study treatment depending on which treatment was taken when the medication was administered. For example, concomitant medication attributed to treatment A will be any medications with start date on or after administration of treatment A but before the administration of the next study treatment or any medications started prior to the instillation of treatment A but had dose or frequency increase after the instillation of treatment A.

Concomitant medications/therapies will be summarized by treatment using WHO Drug Dictionary (WHO-DD) Anatomical-Therapeutic-Chemical Level 2 (ATC-2) classification and preferred term (PT).

[redacted]

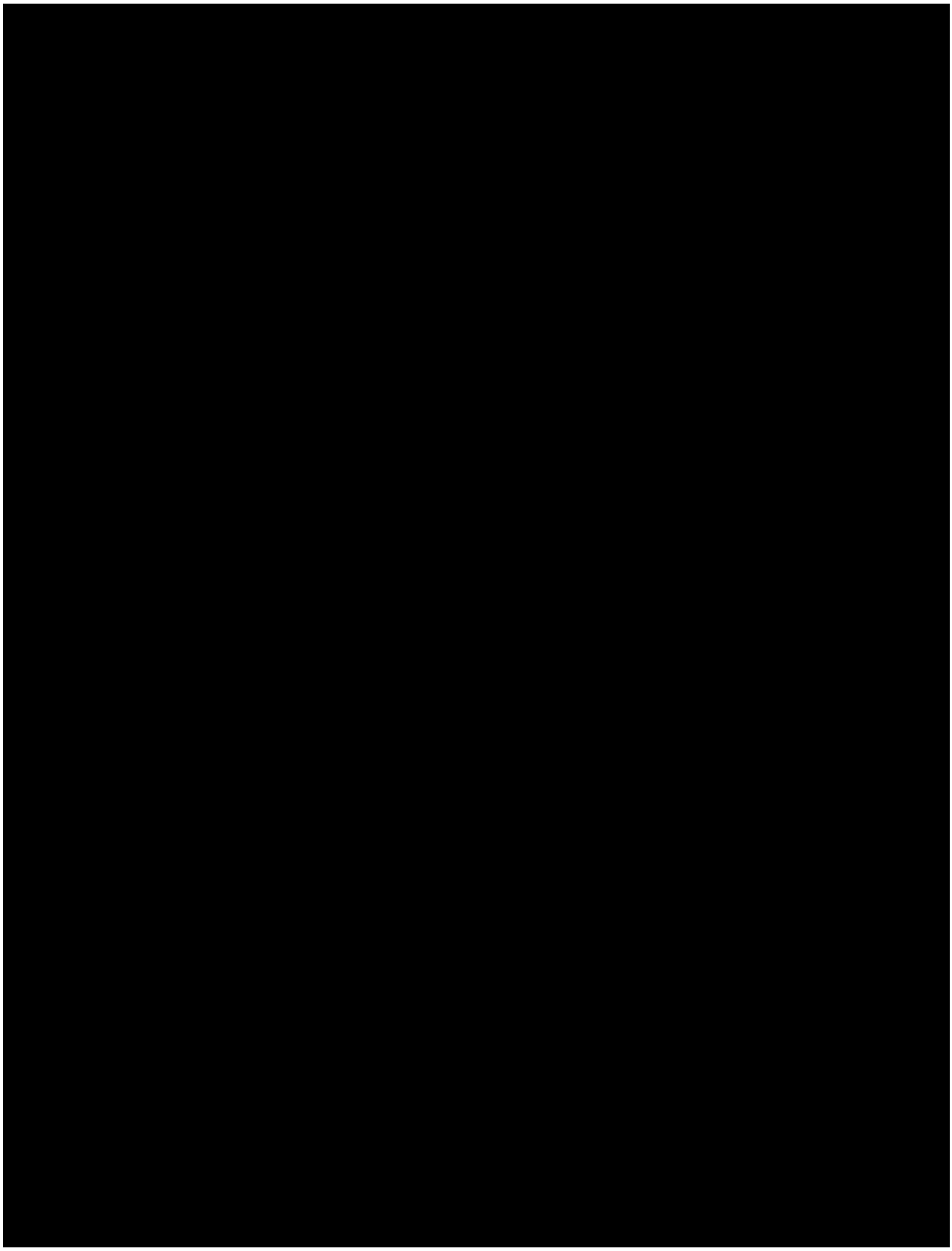
[redacted]

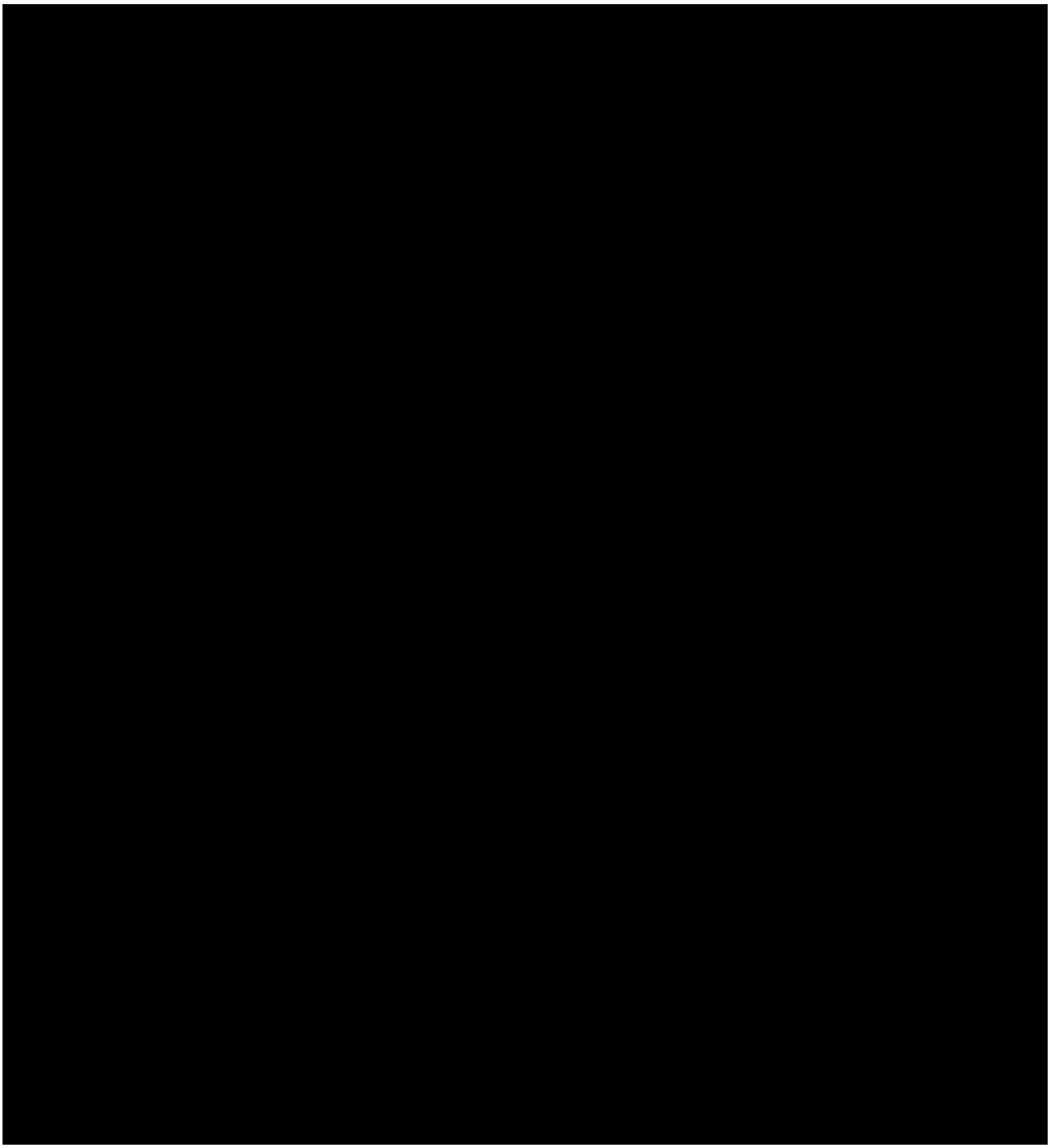
XI. References

1. Carey, V., Zeger, S. L., and Diggle, P. J. (1993). “Modelling Multivariate Binary Data with Alternating Logistic Regressions.” *Biometrika* 80:517–526.
2. EMA/CHMP/44762/2017. “Guideline on multiplicity issues in clinical trials”.
3. Hesterberg TC. (2015). “What Teachers Should Know About the Bootstrap: Resampling in the Undergraduate Statistics Curriculum”. *The American Statistician* 69:4, 371-386, DOI: 10.1080/00031305.2015.1089789.
4. Kenward, M. G., and Roger, J. H. (1997). “Small Sample Inference for Fixed Effects from Restricted Maximum Likelihood.” Biometrics 53:983–997.
5. *Multiple Endpoints in Clinical Trials Guidance for Industry*. US FDA, Jan. 2017, https://www.fda.gov/files/drugs/published/Multiple-Endpoints-in-Clinical-Trials-Guidance-for-Industry.pdf.
6. Rubin DB. Multiple imputation for nonresponse in surveys. New York, NY: John Wiley and Sons; 1987.
7. R J Connor. Sample size for testing differences in proportions for the paired-sample design. Biometrics 1987 Mar;43(1):207-11.
8. SAS Institute Inc: SAS® 9.4 Statements: Reference, Third Edition. Cary, NC: SAS Institute Inc; 2014.

Appendix A - [redacted]

[redacted]





Appendix B - [redacted]

[redacted]

Appendix C – [redacted]

[redacted]